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Risk Factors and Early Detection of Lung Cancer in a Cohort of Chinese Tin Miners

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PURPOSE: To examine risk factors and establish a biologic specimen and data bank for the study of early markers of lung cancer.

METHODS: We designed a dynamic cohort using an ongoing lung cancer screening program among radon- and arsenic-exposed tin miners in Yunnan China. Through the first four years of the study, 8,346 miners aged 40 years and older with over 10 years of occupational exposure have been enrolled, risk factors have been assessed, annual sputum and chest radiographs have been obtained, and numerous biologic specimens have been collected.

RESULTS: A total of 243 new lung cancer cases have been identified through 1995. Radon and arsenic exposures are the predominant risk factors, but lung cancer risk is also associated with chronic bronchitis and silicosis, as well as a number of measures of exposure to tobacco smoke, including early age of first use, duration, and cumulative exposure. Tumor and sputum samples are being examined for early markers of lung cancer.

CONCLUSION: A cohort of occupationally-exposed tin miners with an extensive biologic specimen repository has been successfully established to simultaneously study the etiology and early detection of lung cancer.

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KEY WORDS: Lung Cancer, Radon, Arsenic, Tobacco, Cohort, Early Detection, Biologic Specimen Bank.

INTRODUCTION

Lung cancer is the leading cause of death from malignant neoplasms in the United States and many other countries around the world, with the incidence of, and mortality from, the disease still on the increase in most areas (1, 2). The mortality rates of lung cancer in China vary widely over different regions. Gejiu, a small city in Yunnan Province and the site of the largest Asian tin industry, had the highest male lung cancer mortality rate in all of China in a 1973 nationwide survey. Among the Yunnan miners aged 60–64 years, for example, the annual lung cancer incidence rate exceeded 2,500/100,000 in 1980–84 (3, 4). Between 1973–1993, 1,881 cases of lung cancer were reported at the Yunnan Tin Corporation (YTC). Recent case-control studies identified radon, arsenic, and tobacco as key factors in the etiology of lung cancer in this high risk population (5–7), but dietary inadequacies may also contribute to the excess lung cancer risk (8, 9).

Recent advances in the understanding of the biology of lung cancer suggest that early detection through the systematic application of early markers of lung cancer in sputum should hold great promise for the reduction of lung cancer mortality (10). Numerous candidate markers for the early detection of lung cancer already exist (11–16). Banking serial premalignant specimens from a prospectively-followed high-risk population, along with specimens of subsequent tumors, provides the opportunity to study potential strategies to reduce the incidence and mortality of lung cancer through new methods of early detection (14).

In the current paper, we report the development of a cohort of occupationally-exposed tin miners with an extensive biologic specimen repository that has been successfully

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Selected Abbreviations and Acronyms

YTC = Yunnan Tin Corporation
LIP = Labor Protection Institute
WLM = Working level months
IAEM = Index of Arsenic Exposure Months
SMR = Standardized mortality ratio

established to simultaneously study the etiology and early detection of lung cancer.

MATERIALS AND METHODS

Study Design

Approximately 6,000 tin miners at high risk for lung cancer are screened annually with sputum cytology, chest X-ray, and personal interview as part of a lung cancer screening project that has been conducted by the Labor Protection Institute (LPI) of the YTC since 1973. Lung cancer risk factor information is collected by questionnaire at entry and periodically in follow-up years. Annual sputum specimens and chest X-ray films are stored, and single samples of other biologic specimens (blood, urine, toenails, buccal smear, finger stick blood, as well as tumor and adjacent normal tissue) have also been collected and stored during the follow-up years of the study. Follow-up is also conducted annually during the study to identify all newly diagnosed cancers.

Study Population

The cohort entry criteria are defined as: a) current or retired YTC workers; b) at least 40 years old; c) confirmed history of at least 10 years underground and/or smelting experience; d) no proven active or verified history of previous malignancy (except non-melanoma skin cancer); and e) consenting. The complete study cohort included 8,346 members who participated in the annual screening program at least once between 1992–1995 (7,867 male and 479 female miners). Due to the small proportion of females with 10 years underground mining experience (less than 6%) and the few lung cancer cases (less than 1%), only male workers have been studied in detail here.

Screening Interviews

At the time of study entry, all cohort tin miners are interviewed using a standardized baseline questionnaire. Data are collected on demographic characteristics, residential history, work history, tobacco consumption, diet, family cancer history, and previous medical conditions. Individuals who had smoked cigarettes and/or pipes (water pipes or Chinese long-stem pipes) regularly for six months or longer were asked for information on a variety of smoking-related issues. Dietary information obtained includes a diet history of the frequency of foods consumed during the past year and a single 24-hour food and beverage recall. In order to assure the quality of the questionnaire data, a sample of participants (2%) is re-interviewed each day by supervisory staff. In questionnaires administered in follow-up years, information on tobacco use, diet, and medical status is collected. In a sample of subjects, a diet validation study comparing the diet history food frequency questionnaire to 28 days of diet records was conducted in 1993.

Carcinogen Exposure Levels

The cumulative radon exposure estimate for each subject was obtained by summing across the estimated working level months (WLM) for each job held at the YTC prior to the date of entry at initial screening for both cases, and the non-case members of the high-risk cohort. The cumulative individual worker's exposure to arsenic for each job was estimated by using an index for arsenic exposure (Index of Arsenic Exposure Months or IAEM), which was calculated as a time-weighted average of arsenic concentration (mg/m^3) times exposure months ($mg/m^3 \times$ months). Individuals who had smoked cigarettes and/or pipes (water pipes or Chinese long-stem pipes) regularly for six months or longer at any time in their life were classified as ever smokers and were asked for information on a variety of smoking-related issues. Pack-year equivalents (gram/day $\times$ years $\div$ 20) were used to measure cumulative tobacco consumption which was calculated separately for cigarette (1 cigarette = 1 gram), water, pipe, and long stem pipe, and for total tobacco use.

Chest Radiograph

Single PA chest radiographs are taken and graded by the radiologists of the YTC-LPI Division of Radiology for quality (excellent, good, adequate for interpretation, or unsatisfactory) and diagnostic category (no evidence for lung cancer, suspicious for lung cancer, lung cancer, or unknown/unsatisfactory). Each screening radiograph is read and results recorded independently by two different staff radiologists. Discrepant results are resolved by a referee.

Sputum Cytology

All cohort participants undergo an induction procedure using an ultrasonic nebulizer (DeVilbiss Ultra Neb 200 HI, DeVilbiss Health Inc., Somerset, Pennsylvania) to assist in the production of a satisfactory sputum specimen. A satisfactory induction is defined by the production of 15–20 cc of sputum from deep within the lung (Papanicolaou method). Sputum samples are prepared and stored at room temperature in Saccomanno's preservative (50% ethanol and 2% polyethylene glycol 1450 in distilled water) at the LIP, YTC, in Gejiu. Specimens are smeared on glass slides and stained with Pap's (Papanicolaou's stain) for routine cytopathologic examination at LPI, YTC.

Confirmation of Lung Cancer

Endpoint ascertainment relies on existing clinical methods to identify cases. Because lung cancer and silicosis are designated as occupational diseases at the YTC, case ascertainment is excellent. Approximately 50% of the incident cases are first detected through the annual screening examination. Most of the remaining interval incident cases are identified as they present for diagnostic work-up at the YTC General Workers' Hospital. Additional cases are identified through the YTC cancer registry system, which was established in 1973 and receives information on all YTC cancers from local hospitals. A panel of pathologists, cytologists, radiologists, and clinicians from the LPI and the YTC General Workers' Hospital reviews all suspected cases for evidence of cancer each week. Final review for confirmed diagnosis is performed by a cytopathologist and clinician/epidemiologist from the Johns Hopkins Medical Institutions during their annual site visit. For those having histologic confirmation, cell type is assigned according to the WHO Diagnostic Criteria for Pulmonary Carcinoma (17).

Biological Specimen Collection

In addition to the sputum samples collected and stored at room temperature annually, a one-time collection of additional biologic samples was performed from the second to fourth years of the screening (1993–1995). These samples include 10 ml of whole blood (separated and stored at −84 degrees Centigrade as plasma, red cells, viable lymphocytes, and white cells), a morning urine, buccal smear, finger stick blood, and toenail clippings from each toe. For all lung cancer cases with available histology, paraffin blocks of diagnostic tissue are prepared.

Statistical Methods

Person-years of follow-up for each subject were computed as the amount of time from date of entry at initial screening to date of diagnosis of lung cancer, date of death, or administrative closing date of December 31, 1995 (whichever came first). Lung cancer incidence rates for each age group were calculated by dividing the number of age-specific events by age-specific person-years of follow-up. Total age-adjusted incidence rates were obtained by direct standardization, using the age distribution of the entire high-risk YTC population as a standard.

The calendar-period specific expected numbers of deaths were calculated using the rates from the China national mortality survey (1975) and the age distribution of the whole high-risk YTC population (1992–95). The standardized mortality ratios (SMRs) of observed to expected deaths and 95% confidence intervals (CI) around the SMRs were computed assuming a Poisson distribution (18).

Relative risks and 95% CI for lung cancer risk factors were determined from proportional hazards models using the PHREG procedure in SAS (19).

RESULTS

Lung Cancer among Yunnan Tin Miners

The number of deaths and SMRs for selected causes among YTC miners in the high-risk cohort between 1992–95 are shown in Table 1. Although overall mortality in the YTC high-risk cohort is less than that in the general population (392 vs. 419), excess mortality is seen for cerebrovascular disease and all cancer (17% and 36% of deaths, respectively). Mortality is most striking for lung cancer (28% of all deaths). Some care is appropriate in interpreting these data, however, as expected numbers of deaths were calculated from the only readily available survey data conducted in 1974–76, and any changes in rates since then would influence the SMRs (e.g., an increase in lung cancer rates would increase the number of cases expected, and reduce the SMR).

Table 2 shows a comparison of age-specific lung cancer incidence rates by sex between Yunnan tin miners and the U.S. population. The complete study cohort includes 8,346 members who participated in the annual screening program at least once between 1992–95 (7,867 male and 479 female miners). After 24,733 person years follow-up, 243 new lung cancer cases have been identified through 1995. The distribution of the 174 cases where diagnosis was based on either cytology or histology included 75% squamous cell, 10% adenocarcinoma, 11% small cell, 2% large cell, and 2% other or unknown. For males over 50 years of age, the incidence rate for YTC high-risk male miners was 3–7 times higher than SEER rates for U.S. males (20). For female high-risk miners, only two cases occurred during follow-up, both among women less than 55 years old who had smelter exposure only.

Cohort Participant Characteristics

Table 3 presents the distribution of selected demographic characteristics at the time of initial screening separately for male non-case cohort participants and for lung cancer cases. The total high-risk cohort consists of 7,867 male miners. During almost four years of follow-up in this cohort, 241 new cases of male lung cancer were diagnosed. The median age at time of study entry is 56 years for non-cases and 64 years for lung cancer cases. Age-adjusted case versus non-case cohort comparisons showed that cases were older at time of interview, had lower per capita incomes, had less

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TABLE 1. Number of deaths and SMR for selected causes among the whole Yunnan Tin Mine high-risk cohort, 1992–95

Causes of death (ICD 9th Version)	No. of death Observed	No. of death Expected[a]	SMR	95% CI[b]
Total (000–999)	392	419.0	94	84–103
All cancer (140–239)	140	32.1	436	364–508
Lung cancer (162)	109	3.2	3406	2767–4046
Pulmonary heart dis. (415–416)	41	32.4	127	88–165
Cerebrovascular dis. (430–439)	67	26.8	250	190–310
Others	144	324.5	44	37–52

[a] Calculated using rates from most recent Yunnan Province Mortality Survey (1974–76) and the age distribution of the whole high-risk cohort population (1992–95).
[b] 95% confidence interval on SMR (20).

formal education, were more likely to be retired, and had lower body mass index.

Distributions of self-reported pre-existing medical conditions are shown in Table 4. With the exception of tuberculosis, chronic respiratory diseases were reported more often by cases than the male non-case cohort members. Both chronic bronchitis and silicosis were significantly different, but asthma/hay fever, which differed in crude analyses, was not significantly different after age adjustment. The frequencies of other diseases were similar in the cases and the non-case cohort. For context regarding silicosis, dust levels generally averaged 8.3 to 22.2 mg/m^3 and extensive free silica concentration industrial hygiene measurements performed on the raw ore were considered relatively low, ranging from 0.3 to 1.5% (unpublished data, Labor Protection Institute, Yunnan Tin Corporation).

Table 5 shows the frequency of ever and current tobacco use for the cases and the male non-case cohort. Only four percent of cases and nine percent of the male non-case cohort had never consumed any tobacco product for more than six months. Both the cases and the non-case cohort had similar quit rates for any tobacco (14% vs. 11%). Cigarettes were the most common form of tobacco use reported, followed closely by the water pipe, and distantly by the long stem pipe. Cigarette use was similar in the cases and the total cohort (82% vs. 83%). The prevalence of both water pipe (83% vs. 67%) and long stem pipe (14% vs. 5%) use was slightly higher in the cases, but differences that were evident in crude analyses were not significant after age adjustment.

Detailed tobacco use history among smokers is shown in Table 6. Except for the long stem pipe, the cases started smoking earlier and smoked longer than the non-case cohort. The cases smoked more of any kind of tobacco and cigarettes than the non-case cohort. Among smokers we estimated that 61% of the total lifetime tobacco consumed was in the form of cigarettes, 36% as water pipe, and only 3% as long stem pipe.

Extensive environmental monitoring has been performed over the years for both radon and arsenic exposure, and levels of both exposures have declined markedly since the late 1950s. The average radon daughter exposure level for the workers in this cohort was 1.72 WL. For arsenic, the average air concentration for these workers when mining underground was 0.0189 mg/m^3, while the average air concentration while smelting was 0.486 mg/m^3.

TABLE 2. Comparison of age-specific lung cancer incidence rates between Yunnan tin miners and the U.S. population [Rate per 100,000 (number cases)]

	High-risk YTC cohort (1992–95)		All YTC employees (1989–93)		U.S./SEER population (1986–90)	
Age group	Males	Females	Males	Females	Males	Females
40–44	0 (0)	0 (0)	21	0	17	13
45–49	48 (2)	353 (1)	67	24	48	33
50–54	161 (4)	500 (1)	99	0	108	67
55–59	828 (27)	0 (0)	417	51	192	113
60–64	1122 (61)	0 (0)	1108	0	314	161
65–69	2430 (79)	0 (0)	1345	1079	426	200
70–74	2730 (45)	0 (0)	1602	0	532	233
≥ 75	2923 (23)	0 (0)	1732	0	577	217
Total[a]	885 (241)	170 (2)	280	7	190	51

[a] Total rates are standardized to the total YTC population (1987).

TABLE 3. Age-adjusted relative risks (95% CI) for selected demographic characteristics from the baseline questionnaire for the male YTC high-risk cohort, 1992–95

	%		
Characteristics	Non–case report (n = 7626)	Lung cancer cases (n = 241)	RR (95% CI)
Age at entry (yrs)			
< 60	62.8	19.9	1.00
60–69	29.8	57.7	5.61 (4.04–7.79)
≥ 70	7.4	22.4	9.04 (6.13–13.33)
			$p_{\text{for trend}} = 0.0001$
Retired			
No	47.3	4.6	1.00
Yes	52.7	95.4	4.69 (2.35–9.38)
Education (yrs)			
None	26.1	56.0	1.00
Some (1–5)	33.6	30.3	0.63 (0.47–0.83)
More (≥ 6)	40.2	13.7	0.50 (0.33–0.76)
			$p_{\text{for trend}} = 0.0001$
Per capita income (Yuan)			
Low (< 61)	34.2	46.9	1.00
Median (61–100)	32.8	32.4	0.75 (0.56–1.00)
High (> 100)	33.0	20.8	0.77 (0.56–1.09)
			$p_{\text{for trend}} = 0.08$
BMI (kg/m^2)[a]			
Low (< 20.3)	33.5	47.7	1.00
Median (20.3–22.6)	33.1	29.1	0.91 (0.67–1.23)
High (> 22.6)	33.2	22.8	0.74 (0.53–1.02)
			$p_{\text{for trend}} = 0.07$

[a] There were five non-cases and one case missing data.

Table 7 summarizes lung cancer risk in relation to general work history and specific occupational exposures. After adjustment for age, analysis shows that risk increased with earlier age starting work, greater number of years worked, and more years in jobs exposed to arsenic or radon. Lung cancer risk increased progressively with radon exposure and was in approximately 4-fold for persons in the highest quartile of cumulative radon exposure (i.e., > 577 WLM) compared to the lowest quartile. Lung cancer risk showed a similar increase with arsenic exposure, reaching a relative risk of nearly 5-fold in the highest quartile of cumulative arsenic exposure (> 16.093 IAEM).

Establishment of Biologic Specimen Repository

Table 8 summarizes the biologic specimens and data bank resources collected between 1992–95 for the whole YTC

TABLE 4. Age-adjusted relative risks (95% CI) for selected medical conditions from the baseline questionnaire for the male YTC high-risk cohort, 1992–95

	%		
Characteristic	Non–case cohort (n = 7626)	Lung cancer cases (n = 241)	RR (95% CI)
Asthma/hay fever	8.1	13.7	1.18 (0.82–1.71)
Chronic bronchitis	28.5	48.6	1.73 (1.35–2.24)[a]
Silicosis	5.3	15.4	1.46 (1.02–2.09)[b]
Tuberculosis	3.1	3.7	0.99 (0.51–1.93)
Cardiovascular disease	15.9	17.8	0.82 (0.59–1.13)
Chronic GI disease	29.6	27.4	0.91 (0.69–1.21)
Diabetes	0.5	0.4	0.99 (0.14–7.04)
Kidney disease	7.0	4.6	0.68 (0.37–1.24)
Chronic liver disease	6.4	4.6	0.67 (0.38–1.23)
Family cancer history	8.8	5.8	0.98 (0.57–1.67)

[a] Indicates $p < 0.01$ for age-adjusted comparison by Cox model.
[b] Indicates $p < 0.05$ for age-adjusted comparison by Cox model.

TABLE 5. Age-adjusted relative risks (95% CI) for ever and current tobacco use from the baseline questionnaire for the male YTC high-risk cohort, 1992–95

Tobacco type	% Non–case cohort (n = 7626)	% Lung cancer cases (n = 241)	RR (95% CI)
Any tobacco			
Never	9.3	4.2	1.00
Quit	10.7	13.7	1.33 (0.65–2.71)
Current	80.0	82.2	1.59 (0.84–3.01)
			$p_{\text{for trend}}$ = 0.09
Cigarettes			
Never	16.6	18.3	1.00
Quit	12.6	17.1	1.11 (0.73–1.70)
Current	70.8	64.7	1.32 (0.94–1.85)
			$p_{\text{for trend}}$ = 0.10
Water pipe			
Never	32.6	16.6	1.00
Quit	16.6	22.4	1.01 (0.66–1.55)
Current	50.8	61.0	1.10 (0.77–1.57)
			$p_{\text{for trend}}$ = 0.53
Long stem pipe			
Never	95.0	86.3	1.00
Quit	2.0	7.9	1.67 (1.03–2.71)
Current	3.0	5.8	0.74 (0.43–1.29)
			$p_{\text{for trend}}$ = 0.7

high-risk cohort. A total of 6,259 miners participated in one or more aspects of the year one screening, 6,150 in year two, 6,177 in year three, and 5,939 in year four. Of all 8,764 high-risk miners eligible, 90% participated in screening at least once during this four year period. Of those participating, more than 84% (7,040 of 8,346) participated more than once, including 43% who participated in all four years. Chest X-rays were obtained at 98–99% of screening visits and sputum cytology on 96–98%, depending on the calendar year. For cultural reasons (Chinese consider blood an unreplenishable life fluid), compliance with venous blood collection was lower (50% of subjects). Urine samples were col-

TABLE 6. Age-adjusted relative risks (95% CI) for tobacco use history from the baseline questionnaire for the male YTC high-risk cohort, 1992–95

Any tobacco use	% Non–case cohort (n = 7626)	% Lung cancer cases (n = 241)	RR (95% CI)
Age started (yrs)			
Never	9.3	4.2	1.00
Late (> 20)	25.5	21.6	1.32 (0.67–2.60)
Middle (17–20)	37.2	31.1	1.47 (0.76–2.84)
Early (< 17)	27.9	43.2	1.81 (0.94–3.48)
			$p_{\text{for trend}}$ = 0.02
Years smoked			
None	9.3	4.2	1.00
Low (< 28)	31.0	2.9	0.40 (0.15–1.05)
Medium (28–41)	29.6	22.4	1.46 (0.74–2.87)
High (> 41)	30.1	70.5	2.05 (1.06–3.94)
			$p_{\text{for trend}}$ = 0.0001
Cumulative tobacco smoked (pack-yrs)			
None	9.3	4.2	1.00
Low (< 20)	28.7	19.9	1.19 (0.60–2.36)
Medium (20–34)	32.8	31.1	1.49 (0.77–2.88)
High (> 34)	29.2	44.8	1.88 (0.98–3.60)
			$p_{\text{for trend}}$ = 0.002

TABLE 7. Age-adjusted relative risks (95% CI) for general work history and cumulative occupational exposures from the baseline questionnaire for the male YTC high-risk cohort, 1992–95

Work history and cumulative exposure	% Non–case cohort (n = 7626)	% Lung cancer cases (n = 241)	RR (95% CI)
Age started work			
Q1 (21–41)	26.9	17.0	1.00
Q2 (18–20)	28.0	13.3	1.11 (0.70–1.77)
Q3 (15–17)	22.8	21.2	1.55 (1.02–2.34)
Q4 (6–14)	22.4	48.6	1.78 (1.24–2.56)
			$p_{\text{for trend}} = 0.0005$
Years worked			
Q1 (11–26)	25.5	3.7	1.00
Q2 (27–33)	25.3	11.6	1.13 (0.53–2.43)
Q3 (34–40)	26.7	32.8	1.86 (0.92–3.80)
Q4 (41–78)	22.8	51.9	2.37 (1.15–4.86)
			$p_{\text{for trend}} = 0.0001$
Years exposed (Rn/As)			
Q1 (10–18)	25.4	14.5	1.00
Q2 (19–24)	25.8	14.5	1.27 (0.80–2.04)
Q3 (25–31)	25.4	20.8	1.41 (0.91–2.16)
Q4 (32–56)	23.4	50.2	2.18 (1.50–3.18)
			$p_{\text{for trend}} = 0.0001$
Cumulated radon (WLM)			
Q1 (0–112)	25.6	5.0	1.00
Q2 (113–250)	25.5	10.0	1.60 (0.80–3.19)
Q3 (251–576)	24.9	27.0	2.58 (1.39–4.80)
Q4 (577+)	23.9	58.1	3.91 (2.14–7.17)
			$p_{\text{for trend}} = 0.0001$
Cumulated arsenic (IAEM)			
Q1 (0.062–1.731)	25.7	2.1	1.00
Q2 (1.733–7.287)	25.2	18.7	3.15 (1.23–8.05)
Q3 (7.288–16.090)	24.4	45.2	5.55 (2.21–13.91)
Q4 (16.093+)	24.7	34.0	4.94 (1.95–12.54)
			$p_{\text{for trend}} = 0.0002$

lected only on 43% of subjects, due primarily to a shortage of freezer space rather than acceptability, and toenails were collected on 69% of subjects. Buccal smears and finger stick bloods were widely accepted by YTC mines and serves as an alternative to blood as a source of DNA for future molecular studies. Among the 241 confirmed male lung cancer cases, 174 (72%) had a diagnosis based on either cytology or histology.

DISCUSSION

The extremely high incidence of lung cancer among Yunnan tin miners first attracted international attention in 1984, resulting in several evaluations of the cause and in a feasibility study for a potential chemoprevention trial (5–7, 21, 22). The current project, initiated in 1992, is the first prospective cohort study of lung cancer to focus exclusively on the tin miners with especially high radon and arsenic exposure histories.

The results of analyses reported here substantiate lung cancer as the major health problem in this population. Lung cancer is the leading cause of death, accounting for over one-fourth of all deaths, with incidence rates that are 5- to 7-fold those found in U.S. populations of comparable age, and nearly 34-fold higher than those expected compared to provincial norms. These extraordinary rates combined with the ongoing screening program provided a unique opportunity to evaluate etiology while establishing a biologic specimen repository to evaluate and test the new markers for lung cancer now being identified. With the explosive interest in tumor biology, new tools and strategies have emerged with greater potential to identify markers of lung neoplasia in sputum well in advance of the clinical diagnosis of cancer. The banking of serial premalignant specimens from a high-risk population in conjunction with the collection of specimens of the subsequent tumors provides an opportunity to study potential strategies to reduce the incidence and mortality of lung cancer using new methods of early detection (14). Initial work to evaluate monoclonal antibodies to small cell and non-small cell lung cancer in sputum has begun and is being expanded to examine microsatellite markers and specific mutations. As no previous molecular

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TABLE 8. Biologic specimen and data repository among the whole YTC high-risk cohort, 1992–95

Data or specimen	No. of subjects who had data and specimen at year				
	1992	1993	1994	1995	Total
Baseline questionnaire	6259	1001	614	472	8346
Follow-up questionnaire	n/a	5149	5563	5467	16179
Chest X-ray	6173	5989	5988	5999	24149
Sputum	6148	5852	5897	5913	23810
Venous blood[a]	n/a	2419	1670	105	4194
Urine	n/a	2670	946	1	3617
Toenail	n/a	4638	3566	n/a	8219
Buccal smear	n/a	n/a	n/a	5800	5800
Finger stick	n/a	n/a	n/a	5689	5689
Cohort tissue	9	18	25	6	58
Lung cancer	53	85	48[b]	57	243

[a] Stored as plasma ($n = 4$), red blood cells ($n = 4$), viable lymphocytes ($n = 2$) and white blood cells ($n = 2$) from single 10 ml blood draw.
[b] Includes 2 female miners.

studies of these high-risk miners have been conducted, it will be of substantial interest to determine if the mutational spectrum in these lung cancers parallel those in other countries, and to examine potential genetic fingerprints that may be attributable to radon and arsenic exposure.

An entry criterion for this cohort study is a confirmed history of at least 10 years underground and/or smelting experience. The exposure homogeneity resulting from this criterion limits our ability to evaluate a wide spectrum of radon and arsenic exposures. Relative risks for radon and arsenic exposure, for example, are substantially lower here than in previously reported studies from the entire YTC where the comparison group had lower exposure (5, 23). Despite this homogeneity, marked elevation in lung cancer risk was seen for radon and, especially, arsenic exposure.

Despite the limitation on evaluation of occupational exposures, this cohort provides a good opportunity to study other etiologic factors such as medical conditions, nutritional status, and genetic traits. In previous studies among miners at other locations, excess mortality has been found for nonmalignant respiratory diseases, such as chronic bronchitis, emphysema, asthma, and silicosis (24, 25). In this study, initial results support prior analyses which showed that chronic respiratory diseases were reported more often in persons with lung cancer. Both chronic bronchitis and silicosis were more common in the cases than non-cases, although differences in the prevalence of asthma/hay fever and tuberculosis were not seen. Previous studies in YTC workers have shown that, even after adjustment for occupational exposures, dietary factors appear to play an etiologic role. Reduced risk was seen with increased consumption of vegetables (yellow and light and dark green vegetables, fresh greens, and tomatoes), fruit (bananas), and protein-rich foods (bean curd, eggs, and meat) (8, 9). Future efforts will reexamine these and other dietary factors (e.g., tea consumption) in detail, utilize prediagnostic serum specimens to evaluate a number of biochemical (e.g., antioxidant) hypotheses, and use DNA samples to test for generic polymorphisms that might influence risk.

There are several comparisons of interest between these initial results from the YTC tin mine cohort and those from another tin mine in China (26–28). Dust in the Dachang tin mines in Guangxi is primarily silica, but contains measurable arsenic (0.077–1.62% in ore dust) and cadmium (0.008%), although radon levels are low (0.3 WLM per year). Several analyses based on modest numbers of lung cancer cases (up to 79) in Dachang have found that the number of years exposed to dust underground and smoking are independent risk factors for lung cancer. Silicosis identified by chest X-ray is a risk factor in univariate analysis, but does not appear to be an independent risk factor once dust and smoking exposure are accounted for. While we have not examined levels of dust exposure separately, risk increased monotonically with both the number of years worked and the years exposed to radon and arsenic. Risk also increased with cumulative tobacco smoke exposure. Finally, silicosis appears in age-adjusted analysis to be a lung cancer risk factor at the YTC, but a better understanding of the potential risk from silica will require more detailed assessment of exposure to silica and adjustment for potential confounders (i.e., smoking, arsenic, radon).

CONCLUSION

A dynamic cohort among occupationally-exposed tin miners in China has been established to examine lung cancer risk factors and collect biologic specimens for the study of early markers of lung cancer. Initial analyses indicate that radon and arsenic exposures are the predominant lung cancer risk factors, but risk is also associated with chronic bronchitis and silicosis as well as a number of measures of exposure to tobacco smoke.

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